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EXAMINER	
EMCH, GREGORY S	
ART UNIT	**PAPER NUMBER**
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/669,540	TERKELTAUB, ROBERT	
	Examiner	Art Unit	
	Gregory S. Emch	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3 and 5-15* is/are pending in the application.

4a) Of the above claim(s) *7 and 14* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,5,6,8-13 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) *1-3 and 5-15* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

Claims 1, 2, 5 and 11 have been amended and claim 4 has been canceled as requested in the amendment filed on 12 September 2007. Following the amendment, claims 1-3 and 5-15 are pending in the instant application.

Claims 7 and 14 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to nonelected subject matter, there being no allowable generic or linking claim.

Claims 1-3, 5, 6, 8-13 and 15 are under examination in the instant office action.

Any objection or rejection of record, which is not expressly repeated in this action has been overcome by Applicant's response and withdrawn.

Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

The rejection of claims 1-4 under 35 U.S.C. 112, second paragraph is maintained for reasons of record and as set forth below.

In the reply filed 12 September 2007, Applicant asserts, "Applicant has amended claim 1 to require contacting the cartilage matrix of a subject in need thereof with an inhibitor of activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes in the cartilage matrix. Applicant respectfully

submits that the amended claims now recite the requisite patient population and the specific agents to be administered, and requests withdrawal of the rejection."

Applicant's arguments have been fully considered and are not found persuasive. The claims are indefinite because there is still no direct administration step. Without such, it is unclear to the artisan how the claimed inhibitor will contact the cartilage. In other words, it is unclear how the inhibitor enters into the patient in order to evoke the claimed method. Additionally, because the delivery of the inhibitor is missing, the contacting step is indefinite and thus is open to interpretation as to where the contacting step occurs (e.g. *in vivo* or *ex vivo*). Therefore, the current amendments are still indefinite.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 2, 3, 5, 6 and 8-13 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nurminskaya et al., in view of Hashimoto et al., further in view of Heyninck et al.

Claims 1, 2, 3, 5, 6 and 8-10 are directed to a method for suppressing pathological calcification of the meniscal and articular cartilage matrix, comprising: contacting the cartilage matrix of a subject in need thereof with an inhibitor of activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes in the cartilage matrix, wherein the inhibitor is A20 or NG-monomethyi-L-arginine acetate (NMMA), thereby suppressing pathological calcification in the cartilage matrix. Claims 11-13 are directed to a method for identifying an agent that inhibits matrix calcification, comprising contacting a chondrocyte in vitro with a test agent under conditions for inducing matrix calcification, wherein the chondrocyte expresses zymogen factor XIIIa (FXIIIa) and/or tissue transglutaminase (tTGase); and determining the effect of the test agent on activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes of the cartilage matrix, wherein inhibition of activation and/or activity is indicative of a test agent that inhibits matrix calcification.

The Nurminskaya et al. reference teaches that transglutaminase and FXIIIa are unregulated during chondrocyte hypertrophy and calcification (p.1135) and that these factors are implicated in apoptotic cell death mechanisms in chondrocytes (e.g., p.1136, ¶3, p.1142, ¶5), as in the instant claims 1 and 5. Further, the Nurminskaya et al. reference teaches chondrocytes from a chondrocyte-derived cell line (p.1136, ¶5), as in

the instant claims 10 and 13. Although the teachings of Nurminskaya et al. suggest that blocking activation or activity of tTGase and FXIIIa would decrease apoptosis in pathological states, the reference does not explicitly teach such.

Upon reading the disclosure of the Nurminskaya et al. reference, the skilled artisan would have recognized the desirability of developing improved methods for a treating pathological calcification of the cartilage matrix. Furthermore, the Hashimoto et al. reference teaches that articular and meniscal chondrocyte apoptosis and abnormal articular cartilage matrix calcification and degradation are implicated in human osteoarthritis (pp.1632-1633), as in the instant claim 1. The Hashimoto et al. reference also teaches that future treatment options, (e.g., apoptotic inhibitors), would alleviate chondrocyte apoptosis and thus matrix calcification and degradation (p.1638, final paragraph). The Hashimoto et al. reference teaches that mediators of necrosis and apoptosis in chondrocytes include IL-1, TNFα and nitric oxide (p.1632, ¶3), as in the instant claim 2. Both references teach *in vitro* and *in vivo* methods (entire documents), as in the instant claims 8 and 9, and both references utilize expression vectors to express FXIIIa in chondrocytes (e.g., Nurminskaya et al., p.1137, ¶5, as in the instant claims 12 and 13. Moreover, the Heyninck et al. reference teaches that cellular expression of A20 inhibits TRAF2 mediated NF-κB signal transduction (e.g., abstract), as in the instant claims 3, 5 and 6. The Heyninck et al. reference also teaches that the TRAF2 mediated NF-κB signal transduction pathway is implicated in apoptosis (p.1472, column 1). As evidenced by the prior art, the skilled artisan would have known that inhibiting tTGase and FXIIIa and TRAF2 mediated NF-κB signal transduction to reduce

apoptosis would alleviate disorders of pathological calcification and degradation of the cartilage matrix. Thus, it would have been obvious to the person of ordinary skill to try administration of A20 in an attempt to provide an improved method of treating such disorders and to try to identify agents that affect matrix calcification, (as the instant claim 11), as taught by Hashimoto et al. (p.1638, final paragraph). This is because the artisan has good reason to pursue the known options within his or her technical grasp.

Claim 2 is also rejected under 35 U.S.C. 103(a) as being unpatentable over Nurminskaya et al., in view of Hashimoto et al., further in view of Heyninck et al. and Gohr et al.

The Nurminskaya et al., the Hashimoto et al. and the Heyninck et al. references teach as set forth above.

Upon reading the disclosures of said references, the skilled artisan would have recognized the desirability of developing improved methods for treating pathological calcification of the cartilage matrix (as in human osteoarthritis). Furthermore, the Gohr et al. abstract teaches that S100 proteins are present in aging articular chondrocytes and S100 is a tTGase substrate in these cells. As evidenced by the prior art, the skilled artisan would have known that blocking S100 production in chondrocytes to reduce apoptosis would alleviate disorders of pathological calcification and degradation of the meniscal and articular cartilage matrix. Thus, it would have been obvious to the person of ordinary skill to try to block S100 production in chondrocytes in an attempt to provide

an improved method of treating such disorders. This is because the artisan has good reason to pursue the known options within his or her technical grasp.

Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Nurminskaya et al., in view of Hashimoto et al., further in view of Studer et al.

The claim is directed to a method for identifying an agent that affects matrix calcification, wherein the test agent is a nitric oxide synthase (NOS) inhibitor.

The Nurminskaya et al. and Hashimoto et al. references teach as set forth above.

Upon reading the disclosures of the Nurminskaya et al. and the Hashimoto et al. references, the skilled artisan would have recognized the desirability of developing improved methods for a treating pathological calcification of the cartilage matrix. Furthermore, the Studer et al. reference teaches that inhibitors of NOS relieve the inhibition of cartilage matrix synthesis that occurs in response to IL-1 (abstract). As evidenced by the prior art, the skilled artisan would have known that inhibiting tTGase and FXIIIa and TRAF2 mediated NF-κB signal transduction to reduce apoptosis would alleviate disorders of pathological calcification and degradation of the meniscal and articular cartilage matrix. Thus, it would have been obvious to the person of ordinary skill to try the claimed method of identifying agents that affect matrix calcification as taught by Hashimoto et al. (p.1638, final paragraph) and Studer et al (p.377). This is because the artisan has good reason to pursue the known options within his or her technical grasp.

In the reply filed on 12 September 2007 with regards to the previous rejections under 35 U.S.C. 103(a), Applicant asserts, "that the skilled artisan, on reading Nurminskaya in view of Hashimoto, would not ascertain that inhibiting transglutaminase (tTGase) and zymogen factor (FXIIIa) would result in effectively treating a pathological calcification in cartilage. In fact, Nurminskaya teaches away from the claimed invention in that the Nurminskaya's emphasis for the study of transglutaminase is focused on plasma transglutaminase and not tissue transglutaminase (tTGase)." To summarize Applicant's argument with regards to the Nurminskaya reference, Applicant "asserts that the reference provides no suggestion to arrive at the present invention because: 1) the research in Nurminskaya is focused solely at the role of plasma XIIIa in cellular apoptosis; 2) the role of tissue transglutaminase is so de-emphasized by the Nurminskaya's data that one skilled in the art would believe only plasma XIIIa to be critical in inhibiting cellular apoptosis; and 3) Nurminskaya's overall lack of discussion regarding inhibition of activation of FXIIIa and tTGase. It is also noted that Nurminskaya is directed at examination of cellular apoptosis, not suppressing meniscal and articular cartilage matrix as required by the claimed invention." Applicant further asserts "that the data presented in Hashimoto merely provides a generalized observation that increased chondrocyte apoptosis occurs in cartilage and is correlated with the severity of cartilage degradation. Furthermore, Hashimoto is absolutely silent with regard to any suggestion of using A20 or NMMA to inhibit activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes in the cartilage matrix to suppress pathological calcification in the cartilage matrix." In addition, Applicant "submits that

Heyninck is absolutely silent with regard to using A20 or NMMA to inhibit activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes in the cartilage matrix to suppress pathological calcification in the cartilage matrix."

Applicants' arguments have been fully considered and are not found persuasive.

Regarding Applicants' assertion that the Nurminskaya et al. reference teaches away from the claimed invention, although the reference provides more emphasis on plasma transglutaminase activity it still provides an appreciation of the fact that the tissue form is elevated (p.1141, second column, first paragraph under Discussion). Moreover, it is noted that the three-pronged test for obviousness (i.e., suggestion, motivation and expectation of success in the prior art) is one of a number of rationales that can be used to support a finding of obviousness, as established by KSR. See the recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1396) (available at <http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf>). Rather, an additional rationale for the instant finding of obviousness is that the claims would have been obvious because a person of ordinary skill has good reason to pursue the known options within his or her technical grasp. Thus, the artisan would still at least be motivated to try to inhibit tTGase activation and/or activity. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense.

Regarding Applicant's assertion that Nurminskaya lacks a discussion regarding inhibition of activation of FXIIIa and tTGase, as stated above, the reference teaches that transglutaminase and FXIIIa are unregulated during chondrocyte hypertrophy and calcification (p.1135) and that these factors are implicated in apoptotic cell death mechanisms in chondrocytes (e.g., p.1136, ¶3, p.1142, ¶5). This suggests that blocking activation or activity of tTGase and FXIIIa would decrease apoptosis in pathological states. Regarding Applicant's assertion that Hashimoto provides a generalized observation that increased chondrocyte apoptosis occurs in cartilage and is correlated with the severity of cartilage degradation, this appreciation provides a nexus between the *in vitro* methods disclosed in the Nurminskaya et al. reference and a method of treating human disease. Regarding Applicant's assertion that Heyninck is silent with regard to using A20 or NMMA to inhibit activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes, the reference provides an observation that cellular expression of A20 inhibits TRAF2 mediated NF-κB signal transduction and that the TRAF2 mediated NF-κB signal transduction pathway is implicated in apoptosis (p.1472, column 1). Applicant is reminded that specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involve not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art." See CTS Corp. v. Electro Materials Corp. of America 202 USPQ 22 (DC SNY 1979); and In re Burckel 201 USPQ 67 (CCPA 1979).

Regarding Applicant's assertion that Hashimoto is silent with regard to any suggestion of using A20 or NMMA to inhibit activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase), it is not necessary that the claimed invention be expressly suggested in any one or all of the references to justify combining their teachings; rather the test is what the combined teachings of the references would have suggested to those of ordinary skill in the art See In *re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981).

Also in the reply filed on 12 September 2007, Applicant asserts "Studer merely alleges that there 'is evidence supporting that NO induces apoptosis .... ' (Studer, page 377, paragraph 2). Applicant respectfully asserts that contrary to the Examiner's conclusion regarding the reference, Studer does not teach that NO induces apoptosis in articular chondrocytes but rather discloses" that "apoptosis was *not* observed in iNOS transduced chondrocytes." Furthermore, Applicant alleges that "Gohr is absolutely silent with regard to using A20 or NMMA to inhibit activation and/or activity of zymogen factor (FXIIIa) and tissue transglutaminase (tTGase) in chondrocytes in the cartilage matrix to suppress pathological calcification in the cartilage matrix, as required by the claimed invention."

Applicant's arguments have been fully considered and are not found persuasive. Claim 15 requires identifying an agent that inhibits matrix calcification, wherein the test agent is a nitric oxide synthase inhibitor. The Studer et al. reference teaches that the authors "have...confirmed the ability of the endogenously produced NO to inhibit matrix synthesis" (abstract). Thus, it is irrelevant whether NO causes apoptosis of

chondrocytes; and the reference is deemed proper. Regarding the Ghor reference, as stated above, specific statements in the references themselves which would spell out the claimed invention are not necessary to show obviousness, since questions of obviousness involve not only what references expressly teach, but what they would collectively suggest to one of ordinary skill in the art." See CTS Corp. v. Electro Materials Corp. of America 202 USPQ 22 (DC SNY 1979); and In re Burckel 201 USPQ 67 (CCPA 1979).

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gregory S. Emch whose telephone number is (571) 272-8149. The examiner can normally be reached 9:00 am - 5:30 pm EST (M-F).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey J. Stucker can be reached at (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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18 November 2007

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